UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

JAN - 9 2009

Office of Regulatory Policy
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 6222
Silver Spring, MD 20993-0002

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 5,877,298 was filed on August 15, 2008, under 35 U.S.C. § 156. Please note that Applicant has also applied for patent term extension of U.S. Patent No. 6,696,065 for FDA Ref No. STN BL 125145 for PENTACEL® pursuant to the provisions of 37 C.F.R. § 1.785.

The assistance of your Office is requested in confirming that the product identified in the application, PENTACEL® (DTap-IPV/Hib), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was timely filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to regulatory review under the Public Health Service Act ("PHSA"), or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our preliminary analysis of the application to date indicates that the subject patent would NOT be eligible for extension of the patent term under 35 U.S.C. § 156.

According to the statute:

> (a) The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b) if —
>
> . . .
>
> (5)(A) except as provided in subparagraph (B) or (C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred;
>
> . . . .
>
> (f) For purposes of this section:
>
> (1) The term "product" means:
>
> (A) A drug product.

. . .

(2) The term "drug product" means the active ingredient of—

(A) a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act)

. . .

including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

35 U.S.C. § 156.

Applicant has noted in its application for patent term extension ("PTE application") that each of the active ingredients in PENTACEL® has been previously approved in other vaccines, see pages 5-6 of the PTE application. Furthermore, the Summary Basis for Regulatory Action for PENTACEL® [1] found at http://www.fda.gov/cber/products/pentacel/pentacel062008sbra.htm on the Center for Biologics Evaluation and Research section of the FDA website provides a comparison of the antigens present in PENTACEL® and 3 vaccines, Daptacel®, ActHIB® and PolioVax®, each of which were previously licensed, i.e., approved, in the United States pursuant to section 351 of the PHSA.

According to the Summary Basis for Regulatory Action, PENTACEL® contains

1. diphtheria toxoid
2. tetanus toxoid
3. pertussis toxoid
4. filamentus hemagglutinin
5. fimbriae 2 & 3
6. pertactin
7. poliovirus 1
8. poliovirus 2
9. poliovirus 3
10. PRP-T

Each of the antigens, present in PENTACEL®, has been previously granted permission for commercial marketing or use under section 351 of the PHSA. Specifically, diphtheria toxoid, tetanus toxoid, pertussis toxoid, filamentus hemagglutinin, fimbriae 2 & 3, and pertactin, were previously approved in BLA 103666 in the drug product Daptacel®; PRP-T was previously approved in BLA STN: BL 103935 for the drug product ActHIB®; and Poliovirus 1, poliovirus 2 and poliovirus 3 were previously approved in BLA STN: BL 103940 for the drug product Poliovax®.

The term "product" as used in 35 U.S.C. § 156 includes any new drug or antibiotic drug, as a

---

[1]Accessed on 1/2/2009, a copy of which is attached hereto.

single entity or in combination with another active ingredient. See 35 U.S.C. § 156(f). "For a product which contains a plurality of active ingredients . . . the statute must be analyzed with respect to each active ingredient." See "Request for Patent Term Extension Final Decision," dated March 3, 1994, in U.S. Patent No. 4,529,601 (copy attached). If a drug product contains two active ingredients and both of the active ingredients have been previously approved, then regulatory review of the combination product cannot be relied upon for extension of a patent claiming the approved drug product. See In re Alcon Laboratories, 13 USPQ2d 1115 (Comm'r 1989). Since diphtheria toxoid, tetanus toxoid, pertussis toxoid, filamentus hemagglutinin, fimbriae 2 & 3, pertactin, were previously approved in BLA 103666 for the drug product Daptacel®; PRP-T was previously approved in BLA STN: BL 103935 for the drug product ActHIB®; and poliovirus 1, poliovirus 2 and poliovirus 3 were previously approved in BLA STN: BL 103940 for the drug product Poliovax®, their use in the subject combination product does not appear to comply with 35 U.S.C. § 156(a)(5)(A), *i.e.*, the approval of PENTACEL® would not appear to constitute the first permitted commercial marketing or use of the product as required by 35 U.S.C. § 156(a)(5)(A). Thus, the combination product does not appear to constitute the first permitted commercial marketing or use of any of the active ingredients in the product. U.S. Patent No. 5,877,298 does not appear to be eligible for patent term extension based upon the regulatory review of PENTACEL®. See also Fisons plc v Quigg, 8 USPQ2d 1491 (D.D.C. 1988).

The Federal Circuit confirmed that the Office's position, with respect to the eligibility of combination products having a plurality of active ingredients, is correct, in Arnold Partnership v. Dudas, 362 F.3d 1338, 1343 (Fed. Cir. 2004). In that case, the Court considered whether a patent directed to a combination of active ingredients (ibuprofen and hydrocodone bitartrate) in the drug product VICOPROFEN® would qualify for a patent term extension under § 156 where the active ingredients had each been previously approved separately. *Id.* at 1341. The Court explained that section 156(f) "requires this court to examine a drug product patent's eligibility for extension on a component-by-component basis." *Id.* Doing so, the Court reasoned that section 156(f)

> places a drug product with two active ingredients, A and B, in the same category as a drug product with a single active ingredient. In both instances, those active ingredients individually qualify for examination under the first permitted marketing requirement. **To extend the term of a patent claiming a composition comprising A and B, either A or B must not have been previously marketed.** In other words, at least one of the claimed active ingredients must be new to the marketplace as a drug product.

Id. (emphasis added). The Court then concluded that the patent claiming VICOPROFEN® was ineligible for a patent term extension for failure to comply with 35 U.S.C. § 156(a)(5)(A) because the individual active ingredients of VICOPROFEN®, ibuprofen and hydrocodone bitartrate, had each been previously approved individually. *Id.* at 1342.

The facts here are analogous to those in *Arnold Partnership*. Like the active ingredients ibuprofen and hydrocodone bitartrate in the combination product VICOPROFEN® in *Arnold Partnership*, diphtheria toxoid, tetanus toxoid, pertussis toxoid, filamentus hemagglutinin, fimbriae 2 & 3, pertactin, poliovirus 1, poliovirus 2, poliovirus 3 and PRP-T, have been previously approved in the drug products Daptacel®, ActHIB® and Poliovax®. As a result, the use of diphtheria toxoid, tetanus toxoid, pertussis toxoid, filamentus hemagglutinin, fimbriae 2 & 3, pertactin, poliovirus 1, poliovirus 2, poliovirus 3 and PRP-T in the combination drug product PENTACEL® does not appear to constitute the first permitted commercial marketing or use the product subject to the regulatory review period as required by 35 U.S.C. § 156(a)(5)(A), just as the use of ibuprofen and hydrocodone bitartrate in the combination product VICOPROFEN® did not constitute the first permitted commercial marketing of VICOPROFEN® in *Arnold Partnership*. See *id.* at 1315. Accordingly, U.S. Patent No. 5,877,298 appears to be ineligible for a patent term extension under 35 U.S.C. § 156 and as interpreted in *Arnold Partnership*.

It is the position of the USPTO that the approval for PENTACEL® referenced in the application for patent term extension does not appear to represent approval as "the first permitted commercial marketing or use of the product" as required by § 156(a)(5)(A), and accordingly, U.S. Patent No. 5,877,298 is **ineligible** for extension.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-7755 (telephone) or (571) 273-7755 (facsimile).

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Reza Yacoob
Director, Intellectual Property
Sanofi Pasteur Ltd.
1755 Steeles Ave.
Ontario, Toronto, Canada

Product Approval Information

Summary Basis for Regulatory Action

Date	June 19, 2008
From	Theresa M. Finn, Ph.D
Subject	Summary Basis for Regulatory Action
BLA # Supplement#	125145/0
Applicant	sanofi pasteur, Ltd
Date of Submission	July 26, 2005
PDUFA Goal Date	June 21, 2008
Proprietary Name / Established (USAN) names	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine/ Pentacel
Dosage forms	Liquid. 0.5mL dose Liquid Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus (DTaP-IPV) component to reconstitute lyophilized ActHIB vaccine component (Haemophilus b Conjugate Vaccine [tetanus Toxoid Conjugate])
Proposed Indication(s)	Active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease caused by Haemophilus influenzae type b
Recommended Action:	*Approval*
Signatory Authority(ies) Action	*Offices Signatory Authority:* **Norman W. Baylor, Ph.D.** X□ *I concur with the summary review* □ *I concur with the summary review and include a separate review or addendum to add further analysis* □ *I do not concur with the summary review and include a separate review or addendum*

Specific reviews consulted when preparing this summary are referred to in the text.

Introduction:

Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (DTaP-IPV/Hib, Pentacel) is indicated for active immunization for the prevention of diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to *Haemophilus influenzae* type b. Pentacel consists of a liquid DTaP-IPV component which is used to reconstitute the lyophilized *H. influenzae* type b capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP) conjugated to tetanus toxoid [Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine, ActHIB].

The DTaP-IPV component is manufactured by sanofi pasteur, Ltd. Canada. The ActHIB vaccine component is manufactured by sanofi pasteur, SA, France.

The formulation of Pentacel per 0.5mL dose is presented below:

DTaP- IPV component:
Active Ingredients:
20 µg Pertussis Toxoid (PT)
20 µg Filamentous hemagglutinin (FHA)
5 µg Fimbriae 2 & 3 (FIM)
3 µg Pertactin (PRN)
15 LF Diphtheria toxoid
5 LF Tetanus toxoid
40 DAU poliovirus type 1 (Mahoney)
8 DAU poliovirus type 2 (M.E.F.I.)
32 DAU poliovirus type 3 (Saukett)
10 ug PRP conjugated to 24 ug tetanus toxoid

Adjuvant: 1.5 mg Aluminum phosphate (0.33 mg aluminum)
Excipient: 0.6% (3.3 mg) 2-phenoxyethanol
Tween 80 ~10 ppm
BSA: ≤ 50 ng
Neomycin < 4 pg
Polymyxin B sulphate < 4pg
Formaldehyde: ≤ 0.001% (≤ 5 ug)
Gluteraldehyde: < 100 ppb (< 50 ng)

Act-HIB vaccine component:
10ug polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) conjugated to 24 ug tetanus toxoid
No preservative

The applicant has requested licensure for administration of Pentacel to infants and children 6 weeks through 4 years of age (up to the fifth birthday). Pentacel is administered as a four dose series at 2, 4, 6 and 15-18 months of age. Four doses constitute a primary immunization course against pertussis. Three doses of Pentacel constitute a primary immunization course against diphtheria, tetanus, poliomyelitis and *H. influenzae* type b invasive disease.

Background:

The biologics license application (BLA) for Pentacel was submitted by sanofi pasteur Ltd. Canada on July 26, 2005. A companion supplement (STN ----------. -------
---------- ----------

During review of the file several items of concern were raised:

1. Inconsistent response to the PRP-T (Hib) component of Pentacel. In one pivotal study submitted with the initial BLA submission Pentacel was inferior to the control and in another it was similar to the control. This item was discussed during the Vaccines and Related Biological Products Advisory Committee meeting in January 2005. In October, 2007, sanofi submitted post dose 3 immunogenicity data from another comparative study, in this study non-inferiority of Pentacel was demonstrated relative to separately administered ActHIB.
2. Following vaccination with Pentacel the response to pertactin did not meet the pre-defined criteria for non-inferiority relative to control DTaP vaccines. These data are discussed in detail in the Clinical/Efficacy Section.
3. In 2007, the PT ---------- performed in the sanofi pasteur Canadian laboratory was determined to be non-specific and the ------- values generated were not acceptable to CBER. The applicant provided data to demonstrate that the PT --------- performed in the sanofi pasteur US laboratory was adequate to assess the response to PT in available sera from one of the Pentacel pivotal tudies. These immunogenicity data were submitted to the BLA in December 2007.

Chemistry Manufacturing and Controls Information

The DTaP-IPV component of Pentacel is manufactured in Building --- (DTaP) and -- (IPV and formulation of DTaP-IPV) at sanofi pasteur, Ltd., Canada. The diphtheria toxoid, tetanus toxoid, and pertussis antigens are the same as those used to formulate the applicants DTaP vaccine, DAPTACEL. The inactivated poliovirus antigens are the same as those used to formulate the Poliovirus Vaccine, Inactivated manufactured by sanofi pasteur, Canada (POLIOVAX).

The lyophilized ActHIB vaccine component is manufactured by sanofi pasteur, SA, France. Manufacture of ActHIB is described under STN 103935.

General Manufacturing Summary:

Diphtheria Toxoid:

5

PAGES DETERMINED

TO BE

NOT

RELEASABLE

--- ---

--- --
------------------------------------ --- ---
-- ---
---------------------------------- -------------

--- --
------------------------------------ --- ---
-- --
------------------------------------ ---

--- --
------------------------------------ --- ---
-- ---

Five single dose vials of liquid Pentacel and 5 single dose vials of lyophilized ActHIB are co-packaged in a carton with one package insert.

CBER Lot Release:
CBER will release lots of DTaP-IPV final bulk based upon review of results of in process and final release tests performed by the manufacturer and submitted in the Lot release Protocols. Release of ActHIB vaccine component occurs under STN 103935. The DTaP-IPV component lot release protocols were reviewed and modified following input from the CMC reviewers, CBER lot release staff (OCBQ) and the Division of Product Quality, OVRR.

Facility and Inspection Summary:
The manufacture of the DTaP-IPV component occurs in Buildings --------------------- at sanofi pasteur, Canada. ActHIB vaccine component is manufactured at sanofi pasteur SA, Marcy l'Etoile , France. Labeling and packaging occurs at sanofi pasteur Canada. Pre-approval inspections were waived based on considerations outlined in CBER SOPP 8410 "Determining when Pre-Licensing/Per-Approval Inspections (PLI/PAI) are necessary." See June 2008 memo from N. Waites.

Environmental Assessment:
A categorical exclusion from filing an environmental assessment was requested by sanofi pasteur and granted. See memo from N. Waites in the Inspection tab.

Clinical

Summary of Effectiveness (Immunogenicity)

Table 9 shows the antigen composition of Pentacel and comparator vaccines that were used in pivotal controlled clinical studies. HCPDT is a non-US-licensed DTaP vaccine which contains the same quantities of pertussis antigens, diphtheria and tetanus toxoids as contained in Pentacel. DAPTACEL, also manufactured by sanofi pasteur Ltd. contains the same diphtheria and tetanus toxoids and pertussis antigens as Pentacel and HCPDT but with reduced quantities of PT and FHA as compared to these vaccines. POLIOVAX (sanofi pasteur Ltd) and IPOL (sanofi pasteur SA) are US-licensed inactivated poliovirus vaccines. The poliovirus components of Pentacel are the same as those in POLIOVAX. For manufacture of POLIOVAX the polioviruses are grown in MRC-5 cells. For manufacture of IPOL, the polioviruses are grown in VERO cells.

Table 9: Antigen composition of Pentacel, HCPDT, ActHIB, POLIOVAX, DAPTACEL and IPOL (per dose):

Antigen	Pentacel	HCPDT[1]	DAPTACEL[2]	ActHIB[3]	POLIOVAX[4]	IPOL[5]
Diphtheria toxoid	15 Lf	15 Lf	15 Lf	-	-	-
Tetanus toxoid	5 Lf	5 Lf	5 Lf	-	-	-
Pertussis toxoid	20ug	20ug	10ug	-	-	-
Filamentous hemagglutinin	20ug	20 ug	5 ug	-	-	-
Fimbriae 2 & 3	5 ug	5 ug	5 ug	-	-	-
Pertactin	3 ug	3 ug	3 ug	-	-	-
Poliovirus 1	40 DAU	-	-	-	40 DAU	40 DAU
Poliovirus 2	8 DAU	-	-	-	8 DAU	8 DAU
Poliovirus 3	32 DAU	-	-	-	32 DAU	32 DAU
PRP-T	10 ug (+ 24 ug tetanus toxoid)	-	-	10 ug (+ 24 ug tetanus toxoid)	-	

1 HCPDT: DTaP manufactured by Sanofi Pasteur Limited; not licensed in the U.S.
2 DAPTACEL DTaP manufactured by Sanofi Pasteur Limited; licensed in the U.S.
3. ActHIB: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur SA
4 POLIOVAX: Poliovirus Vaccine Inactivated, Sanofi Pasteur Limited
5 IPOL: Poliovirus Vaccine Inactivated, Sanofi Pasteur S.A.
DAU = D-antigen Units
PRP-T = polyribosyl-ribitol-phosphate conjugated to tetanus toxoid
Source: Compiled by FDA reviewer.

The Pentacel BLA contains four pivotal immunogenicity studies: 494-01, 494-03, P3T06 and 5A9908.

These studies evaluated lot consistency, non-inferiority relative to separately administered control vaccines and the effect of Pentacel on concurrently administered recommended vaccines. In addition, a serological bridge of pertussis immune responses following Pentacel administered in Study 494-01 to the response to DAPTACEL in the Sweden I efficacy trial was provided. Summary data from one supportive study, M5A07, designed to assess the effect of Prevnar on the response to Pentacel antigens were provided. Additional anti-PRP immunogenicity data from Study M5A10 were provided during review of the application. Results and conclusions based on data submitted in the application are summarized in this section.

Efficacy of Pentacel

Evaluation of the effectiveness of the tetanus, diphtheria, polio and PRP-T components of Pentacel was based on a comparison of immune responses, using established correlates of protection and for some antigens, geometric mean antibody titers (GMTs) or geometric mean antibody concentrations (GMCs), relative to separately administered vaccine components (HCPDT+ POLIOVAX + ActHIB) or all U.S. licensed vaccines (DAPTACEL + IPOL + ActHIB) in US children. The evaluation of the effectiveness of the pertussis component, which does not have a generally accepted correlate of protection, was based on: 1) a comparison of immune responses following four doses of Pentacel in U.S. children to responses following three doses of DAPTACEL in the Sweden I efficacy Trial, and 2) a comparison of immune responses following Pentacel relative to DAPTACEL in US children.

The Pentacel BLA contains two studies comparing the immune response of Pentacel to that of separately administered control vaccines: Study 494-01 evaluated non-inferiority of Pentacel antigens relative to separately administered HCPDT, ActHIB and POLIOVAX. In Study P3T06 control subjects were administered DAPTACEL, ActHIB and IPOL. In this study non-inferiority was evaluated for the response to diphtheria, tetanus, pertussis and PRP-T components. During review of the application summary data from Study M5A10 was submitted to support effectiveness of the PRP-T component of Pentacel.

Polio virus type 1, 2 and 3

Following three doses of Pentacel in Studies 494-01 and P3T06, >99% of subjects had protective neutralizing antibody against each poliovirus serotype.

Diphtheria and tetanus toxoids

Based on review of post-dose 3 anti-tetanus toxoid levels measured using the sanofi pasteur-US ELISA and assessment of the ability of these sera to neutralize tetanus toxin in the ---------- assay ELISA anti-tetanus toxoid levels $\geq$ 0.1 IU/mL are considered the minimum protective level.

Literature data indicate that an anti-diphtheria toxin level $\geq$0.01 IU/mL is the lowest giving some degree of protection while a level $\geq$0.1 IU/mL may be needed for full protection.

Following three doses of Pentacel in Study 494-01 and P3T06, >99% of subjects had an anti-tetanus toxoid level $\geq$0.1 IU/mL and >99% had an anti-diphtheria toxin level $\geq$0.01 IU/mL. Following three doses of Pentacel in Study 494-01 92 % of subjects had an anti-diphtheria toxin level $\geq$0.1 IU/mL.

PRP-T

Anti-PRP has been shown to correlate with protection against invasive *H. influenzae* type b (Hib) disease. Based on efficacy studies with Hib polysaccharide (not Hib-conjugate) vaccines and data from passive antibody studies, a post-vaccination anti-PRP level of 0.15 µg/ml has been accepted as correlating with at least short-term protection[1] and 1.0 µg/ml with long-term (one year) protection[2,3]. Although the relevance of these levels to PRP conjugate vaccines is not entirely clear, they have been

used to evaluate the effectiveness of PRP conjugate vaccines and combination vaccines containing PRP components.

The immune response following three doses of ActHIB or Pentacel in the pivotal studies and additional studies is summarized in Table 10. All anti-PRP assays were performed by sanofi pasteur-US in either Building ----------

In the two comparative pivotal studies, Pentacel was non-inferior to separately administered ActHIB with regard to post-dose 3 anti-PRP levels ≥0.15 µg/ml. However, these two studies showed contradictory results with regard to anti-PRP levels ≥1.0 µg/ml and GMCs:

In Study 494-01 the proportion of subjects with anti-PRP levels ≥1.0 µg/ml and the GMC were lower following three doses of Pentacel compared to three doses of separately administered ActHIB. In Study P3T06 the proportion of subjects with anti-PRP levels ≥1.0 µg/ml and the GMC were similar following three doses of Pentacel or separately administered ActHIB. However, the anti-PRP responses following both Pentacel and ActHIB in Study P3T06 were lower than observed in Study 494-01, with the most notable differences in the ActHIB arms of the two studies (e.g., post-dose 3 GMT 2.29 µg/ml for Study P3T06 and 6.23 µg/ml for Study 494-01).

In comparative Study M5A10 the anti-PRP response following three doses of Pentacel or separately administered ActHIB was similar.

In studies which did not include an ActHIB comparator (Studies 494-03 and M5A07), following the third dose of Pentacel, the anti-PRP GMC ranged from 2.8-3.6 µg/ml and the proportion of subjects with PRP antibody levels ≥ 1.0 µg/ml ranged from 75.6-79.6%, consistent with the Pentacel arms of the comparative studies.

Table 10: Response to PRP-T following three doses of Pentacel or ActHIB in Pivotal and supportive BLA studies –assays performed at Aventis –US Blg-- (shaded cells) or Blg -- (not shaded cells)

	Pentacel					
Study	**Study 494-01 (N=1127)**	**494-03 (n = 270)**	**P3T06 (N=365)**	**M5A07 (P+P) (N=433)**	**M5A07 (P-P) (N=427)**	**M5A10 (N=826)**
Post dose 3						
% ≥0.15 µg/mL	95.4 (94.0, 96.5)	94.4 (91.0, 96.9)	92.3 (89.1, 94.8)	95.8 (93.5, 97.5)	95.3 (92.9, 97.1)	93.8 (92.0, 95.4)
% ≥1.0 µg/mL	79.1 (76.7, 81.5)	75.6 (70.0, 80.6)	72.1 (67.1, 76.6)	77.1 (72.9, 81.0)	79.6 (75.5, 83.3)	75.1 (72.0, 78.0)
GMC	3.19 (2.91, 3.50)	2.80 (2.30, 3.41)	2.31 (1.94, 2.75)	3.32 (2.85, 3.87)	3.60 (3.09, 4.20)	2.52 (2.25, 2.81)
Pre-dose 4	(N=829)		(N = 335)			

% ≥0.15 µg/mL	68.6 (65.4, 71.8)	NA	65.4 (60.0, 70.5)	NA	NA	NA
ActHIB Vaccine						
Study	**494-01 (N=401)**		**P3T06 (N=1128)**			**M5A10 (N = 421)**
Post dose 3						
% ≥0.15 µg/mL	98.3 (96.4, 99.3)		93.3 (91.6, 94.7)			90.3 (87.0, 92.9)
% ≥1.0 µg/mL	88.8 (85.3, 91.7)		70.8 (68.1, 73.5)			74.8 (70.4, 78.9)
GMC	6.23 (5.40, 7.18)		2.29 (2.08, 2.53)			2.38 (2.01, 2.81)
Pre-dose 4	(N = 276)		(N = 323)			
% ≥0.15 µg/mL	80.8 (75.6, 85.3)		60.7 (55.1, 66.0)			NA

494-01 pooled Pentacel data, P3T06 pooled DAPTACEL + ActHIB groups
M5A07 (P+P) Pentacel administered concurrently with Prevnar, M5A07 (P-P) Prevnar administered 1 month after each dose of Pentacel.
Source: Compiled by FDA reviewer.

In Studies 494-01 and P3T06, the post-dose 3 anti-PRP responses appeared to influence the proportion of subjects with seroprotective levels at 15 months of age prior to receipt of a fourth dose of PRP-T: In Study 494-01 67% of subjects administered Pentacel had anti-PRP levels ≥0.15 µg/ml compared with 81% of subjects administered ActHIB separately. At 15-16 months of age prior to administration of the fourth dose of PRP-T, 61-65% of P3T06 subjects had anti-PRP levels ≥0.15 µg/ml.

Sanofi pasteur and CBER have considered whether the anti-PRP immune response seen in Pentacel studies is consistent with previous ActHIB experience. CBER has also considered whether the observed variability in anti-PRP responses may be due to differences in assays, lot-to-lot variability, co-administered vaccines and/or the race/ethnicity of subjects. Discussion of these items may be found in the Conclusions section of the Immunogenicity review.

Pertussis antigens
The efficacy of three doses of DAPTACEL (2, 4, and 6 months) against pertussis was demonstrated in a clinical study in Swedish infants (Sweden I). Following three doses of DAPTACEL in US infants, antibody responses to PT, FHA and FIM were similar to those observed in the Swedish infants. The immune response to pertactin (seroconversion rates [proportion of subjects with a four-fold rise in antibody level following vaccination relative to pre-vaccination level] and GMCs) following three doses

in US infants was significantly lower than in Swedish infants. The antibody responses to all pertussis antigens in North American infants after four doses of DAPTACEL (2, 4, 6, and 17-20 months) were comparable to those achieved after three doses in Swedish infants. Based on these data, four doses of DAPTACEL constitute a primary immunization course for pertussis in U.S. children.

Because the pertussis antigens of Pentacel are the same as those contained in DAPTACEL, effectiveness of the pertussis component of Pentacel was evaluated by comparison of the immune response of US-children administered Pentacel to that of infants administered DAPTACEL. The response to the FHA, FIM and pertactin antigens following four doses of Pentacel in Study 494-01 was compared to the response of infants administered three doses of DAPTACEL in the Sweden I efficacy study. The PT ---- -- performed at the sanofi pasteur, Canada, laboratory was determined to be non-specific thus, a comparison of anti-PT levels are not available for this serology bridge analysis. Immunogenicity of the pertussis component of Pentacel compared to DAPTACEL was also evaluated in Study P3T06 following three and four doses of each vaccine. A comparison of anti-PT levels was only available for a subset of sera from this study which were reassayed in the laboratory of sanofi pasteur, U.S.

Serology bridge to Sweden I Although not pre-specified as non-inferiority analyses, the immune response to FIM and pertactin was diminished following three doses of Pentacel in Study 494-01 compared to three doses of DAPTACEL in Sweden I. Following four doses of Pentacel compared to three doses of DAPTACEL in Sweden I non-inferiority was demonstrated for, FHA and FIM seroconversion rates and GMCs for FHA, FIM and pertactin. Non-inferiority was not demonstrated for pertactin seroconversion rates (89.2% vs. 98.8%; UL of 95% CI for difference DAPTACEL minus Pentacel = 13.2%).

Study P3T06 Following three doses of each vaccine, non-inferiority of Pentacel relative to DAPTACEL was demonstrated for seroconversion rates and GMT for all pertussis antigens. Following four doses of each vaccine, non-inferiority of Pentacel relative to DAPTACEL was demonstrated for seroconversion rates for all antigens and GMT for PT, FHA and FIM. Although the quantity of pertactin in both vaccines is the same, the post-dose 4 GMT to pertactin was significantly diminished in Pentacel recipients as compared to DAPTACEL recipients (93.6 EU/mL vs. 186.1 EU/mL; UL of 90% CI for GMT ratio DAPTACEL/Pentacel = 2.25).

Reduced response to Pertactin
In the absence of a correlate for pertussis protection the clinical significance of a diminished response to pertactin is unclear. The BLA contains a number of analyses to investigate potential explanations and implications for the reduced response to pertactin following Pentacel.

Lot consistency
Study 494-01 evaluated consistency of manufacture of three lots of Pentacel through analysis of seroprotection/seroresponse rates and GMT response to each of the antigens contained in Pentacel. Equivalence was demonstrated for seroconversion/seroprotection rates for PRP, FHA, FIM, pertactin, diphtheria and tetanus toxoids and polio virus serotypes. Equivalence was demonstrated for the GMC to FHA, FIM, pertactin, diphtheria and tetanus toxoids. Equivalence criteria were not met with regard to GMC for PRP and GMT for polio virus serotypes however; CBER considered this in the context of demonstration of lot-consistency for rates of seroprotective antibody levels for these antigens and concluded there were no major concerns with respect to lot consistency.

Because the PT ------ values used for evaluation of lot consistency were generated in the assay performed at sanofi pasteur, Canada, data are not available to support lot consistency of the PT antigen of Pentacel.

Response to co-administered vaccines

Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRN_{197} Protein), (Prevnar, Wyeth Pharmaceuticals Inc.)

In Study P3T06 Prevnar was administered with control, standard of care vaccines or Pentacel at 2, 4 and 6 months of age. Protective levels of antibody to pnuemococcal polysaccharides have not been determined, based on advice provided to the applicant by CBER at the time the study was conducted the proportion of subjects with antibody levels $\geq$0.15 ug/mL and $\geq$0.5 ug/mL to each of the pneumococcal serotypes was evaluated. In P3T06 following three doses of Prevnar administered with Pentacel or control vaccines the proportion of subjects with antibody levels $\geq$0.15 ug/mL and $\geq$0.5 ug/mL to each of the pneumococcal serotypes appeared similar in both groups. Similarly, the GMC to each of the serotypes appeared similar between groups.

In Study 494-03 a comparison of antibody levels $\geq$0.15 ug/mL and $\geq$0.5 ug/mL, and GMC to each of the pneumococcal serotypes following a fourth dose of Prevnar administered with Pentacel or administered with MMR and varicella at 15 months of age demonstrated non-inferiority for each comparison. All subjects in this study had received three previous doses of Prevnar concomitantly administered with Pentacel.

No data are available on responses to the first three doses of Prevnar administered concomitantly with or at different times from Pentacel.

Hepatitis B Vaccine Recombinant (RECOMBIVAX HB, Merck & Co., Inc.)

In Studies 494-01 and P3T06 RECOMBIVAX HB was administered concomitantly with Pentacel at 2 and 6 months of age. Children enrolled in these studies received their first dose of hepatitis B vaccine prior to enrollment in the study. In Study 494-03 receipt of a birth dose of hepatitis B was not an inclusion criterion; subjects who had received a birth dose of hepatitis B vaccine were administered RECOMBIVAX HB concomitantly with Pentacel at 2 and 6 months of age while subjects who had not received a birth dose were administered RECOMBIVAX HB concomitantly with Pentacel at 2, 4 and 6 months of age. The hepatitis B vaccines administered at birth were not recorded. Across these three pivotal studies, 89.8%-100% of subjects achieved a protective level of anti-HBsAg following the third dose of hepatitis B vaccine. Within each comparative study the response to hepatitis B vaccine when coadministered with Pentacel appeared similar to that observed when administered with control vaccines.

Measles, Mumps, and Rubella Virus Vaccine Live (MMR_{II}, Merck & Co., Inc.) and Varicella Virus Vaccine Live (Oka/Merck) (VARIVAX, Merck & Co., Inc.)

A secondary endpoint of Study 494-03 was an evaluation of the response to MMR_{II} and varicella vaccine when administered with Pentacel compared to the response when these vaccines were administered with Prevnar at 15 months of age. Co-administration of MMR_{II} and VARIVAX with Pentacel did not adversely affect the seroresponse rates for measles, mumps, rubella or varicella.

Rotavirus Vaccine, Live, Oral, Pentavalent (Rotateq Merck & Co., Inc.) and Rotavirus Vaccine, live, Oral (ROTARIX, GlaxoSmithKline Biologicals)

Rotateq and ROTARIX were approved February 3, 2006, and April 3, 2008, respectively. No data submitted to the BLA address co-administration of Pentacel with rotavirus vaccine.

Canadian Epidemiologic Data

The BLA contains Canadian epidemiologic data from post-marketing experience in Canada, submitted in support of efficacy of the PRP-T and pertussis components of Pentacel.

Effectiveness Conclusions and Recommendations
Following three doses of Pentacel over 99% of subjects had seroprotective antibody levels to diphtheria and tetanus toxoids and poliovirus types 1, 2, and 3. Based on these data and non-inferiority analyses the effectiveness of the diphtheria, tetanus and polio components of Pentacel can be expected to be similar to that of separately administered control vaccines.

The data to support the effectiveness of the PRP-T component are inconsistent: In one study the immune response to the PRP-T component of Pentacel was diminished as compared to separately administered ActHIB. In two comparative studies non-inferiority was demonstrated however, the response to separately administered ActHIB was lower than expected based on historical data. These studies provide evidence that the effectiveness of the PRP-T component of Pentacel against invasive Hib disease is expected to be similar to that of currently administered ActHIB in the US.

Four doses of Pentacel were expected to constitute the primary immunization series for pertussis. However, the response to the pertussis antigen, pertactin, was diminished following Pentacel as compared to control vaccines. The clinical relevance of this diminished response is unknown.

Safety

Provided by K. Farizo

The Pentacel BLA included safety data from four pivotal studies, in which a total of 5,980 subjects received at least one dose of Pentacel.* Of these subjects, 4,198 were enrolled in one of three U.S. studies (494-01, 494-03, and P3T06) that evaluated four consecutive doses of Pentacel administered at 2, 4, 6 and 15-16 months of age. In Study 5A9908, conducted in Canada, 1,782 subjects previously vaccinated with three doses of Pentacel, received a fourth dose at 15-18 months of age. Overall, across the four studies, 17,021 doses of Pentacel were administered.

In two pivotal studies, the safety of Pentacel was compared to separately administered vaccines: HCPDT (DTaP manufactured by Sanofi Pasteur Limited; not licensed in the U.S.), POLIOVAX (Poliovirus Vaccine Inactivated, Sanofi Pasteur Limited) and ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur SA] in Study 494-01; and DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Sanofi Pasteur Limited), IPOL (Poliovirus Vaccine Inactivated, Sanofi Pasteur SA) and ActHIB in Study P3T06. With the exception of HCPDT, all control vaccines are licensed in the U.S. For Study 494-01, which was initiated prior to licensure of DAPTACEL in the U.S., CBER agreed to the use of HCPDT as the control DTaP vaccine. HCPDT is identical to the DTaP component of Pentacel and differs from DAPTACEL only in its higher content of detoxified PT and FHA. Safety data on HCPDT were considered supportive for licensure of DAPTACEL in the U.S. Under the DAPTACEL BLA, CBER reviewed data on serious adverse events from the Sweden II Efficacy Trial in which approximately 20,000 infants received HCPDT, predominantly at 3, 5, and 12 months of age; a subset of approximately 2,500 subjects received HCPDT at 2, 4, and 6 months of age. In addition, the DAPTACEL BLA included comparative safety data on more common adverse events following HCPDT or DAPTACEL from smaller studies. Data from the Sweden II Efficacy Trial on serious adverse events following HCPDT were included in the Pentacel BLA and are presented in Section 6.7 of CBER's Clinical Safety Review of Pentacel.

In the three pivotal safety studies in which subjects received four consecutive doses of Pentacel, Prevnar [Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRN_{197} Protein), Wyeth Pharmaceuticals Inc.] was administered concomitantly with the first three doses of Pentacel in most subjects. The second and third doses of the hepatitis B vaccine series, using RECOMBIVAX HB (Hepatitis B Vaccine

Recombinant, Merck & Co., Inc.), also were administered concomitantly with the first and third doses of Pentacel in most subjects. In one study, some subjects who had not previously received the first dose of hepatitis B vaccine received three doses of RECOMBIVAX HB concomitantly with the first three doses of Pentacel. Depending on the study design, in the pivotal safety studies, the fourth dose of Pentacel was given either alone, concomitantly with the first doses of MMR II (Measles, Mumps, and Rubella Virus Vaccine Live, Merck & Co., Inc.) and VARIVAX [Varicella Virus Vaccine Live (Oka/Merck), Merck & Co., Inc.], or concomitantly with the fourth dose of Prevnar. The pivotal safety studies of Pentacel were conducted prior to licensure of the two currently licensed Rotavirus vaccines in the U.S., and thus, did not evaluate the safety of Pentacel administered concomitantly with either of these vaccines.

Overall, the quality of the safety data from the pivotal safety studies was adequate to assess the safety of Pentacel.

In the two controlled pivotal safety studies, overall rates of serious adverse events were similar in Pentacel and Control subjects. These studies were not designed to reliably evaluate differences between groups with regard to particular serious adverse events. Across the pivotal safety studies, following Doses 1-3 combined of Pentacel or Control vaccines, the most frequently reported serious adverse events were bronchiolitis, dehydration, pneumonia and gastroenteritis. Across the pivotal safety studies, following the fourth dose of Pentacel or Control vaccines, the most frequently reported serious adverse events were dehydration, gastroenteritis, asthma, and pneumonia.

A total of five deaths occurred during the pivotal safety studies: four among subjects who received Pentacel (N=5,979) (asphyxia due to suffocation, head trauma, SIDS, and neuroblastoma, respectively) and one in a subject who received DAPTACEL, IPOL and ActHIB separately (N=1,455) (aspiration and metastatic ependymoma).

Two cases of encephalopathy occurred during the pivotal safety studies. One case was secondary to cardiac arrest following cardiac surgery 30 days after Pentacel. One case occurred in an infant who developed neurological symptoms 8 days following Pentacel, had structural cerebral abnormalities on MRI, and was eventually diagnosed with congenital encephalopathy.

In the pivotal safety studies, there were no febrile seizures within seven days following any of Doses 1-3 of Pentacel (N=4,197 subjects) or Control vaccines (HCPDT, POLIOVAX and ActHIB: N=1,032 subjects; DAPTACEL, IPOL and ActHIB: N=1,455 subjects). One subject experienced a possible seizure on the same day as the third dose of Pentacel and also had fever reported the same day. Four subjects experienced a febrile seizure within seven days following the fourth dose of Pentacel or Control vaccines: 2 of 5,033 Pentacel subjects, 2 of 739 subjects who received HCPDT, POLIOVAX and ActHIB separately, and 0 of 418 subjects who received DAPTACEL, IPOL and ActHIB separately. Overall, there were three afebrile seizures within seven days following any of Doses 1-3 of Pentacel or Control vaccines: one each following Pentacel; HCPDT, POLIOVAX, and ActHIB administered separately; and DAPTACEL, IPOL, and ActHIB administered separately. There were no afebrile seizures within seven days following the fourth dose of Pentacel or Control vaccines.

Across the four pivotal safety studies, no cases of hypotonic hyporesponsive episodes (HHEs) meeting the pre-specified definition were reported following any dose of Pentacel (N=5,979 subjects) or Control vaccines (HCPDT, POLIOVAX and ActHIB: N=1,032 subjects; DAPTACEL, IPOL and ActHIB: N=1,455 subjects).

With regard to fever and other commonly occurring solicited local and systemic adverse events, no notable increases in rates following Pentacel relative to separately administered Control vaccines were

identified. Compliance with measuring temperature rectally following Doses 1-3 of Pentacel or Control vaccines, as specified in the protocols, was relatively low (approximately 50% of measurements). In one study in which temperatures were also to be taken rectally following the fourth dose, approximately one-third of measurements post-Dose 4 were rectal. In the two controlled studies, use of different routes of temperature measurement was similar in Pentacel and Control subjects. Whether infants had medical visits for fever was not specifically solicited or systematically assessed in the pivotal studies.

In addition to safety data from four pivotal studies, the BLA included supportive safety data from eight historical non-IND studies (six studies conducted in Canada and one each in Israel and Mexico). None of these studies included a control group that received a U.S. licensed DTaP vaccine or HCPDT. In three studies, a total of 996 subjects previously vaccinated with three doses of whole cell DTP vaccine received a single dose of Pentacel. In the other studies, a total of 1,694 subjects received three or four consecutive doses of Pentacel. The types of serious adverse events reported were generally similar to those reported in the pivotal studies.

The BLA also included supportive post-marketing safety data on Pentacel, reflecting a 9-year period between 5/1/97 and 4/30/06, during which a total of approximately 13.5 million doses of Pentacel were distributed outside the U.S., 92% of them in Canada. In Canada, Pentacel administered at 2, 4, 6, and 18 months of age and Sanofi Pasteur's DTaP-IPV administered at 4-6 years of age replaced whole-cell DTP vaccines and have been used exclusively since 1997-1998 to prevent pertussis, poliomyelitis and invasive Hib disease throughout early childhood. Post-marketing safety data presented in the BLA included spontaneous reports received by Sanofi Pasteur, the results of a retrospective survey for adverse events following the fourth dose of Pentacel conducted in approximately 3,000 children in British Columbia, and publications from an active surveillance system for adverse events following vaccination.

During the 9-year post-marketing period, Sanofi Pasteur received 288 adverse event reports following Pentacel. Most events reported in the post-marketing setting also have been reported in clinical trials of Pentacel. The five most frequently reported events in the post-marketing setting were injection site reaction, pyrexia, crying, injection site inflammation and irritability. During the 9-year period, there were 14 post-marketing reports of deaths, including five cases of SIDS, four other deaths without known cause, two deaths due to Hib meningitis following the first dose of Pentacel, and one death each due to Group B streptococcal sepsis, congenital anomalies, and seizures. For all 14 reported deaths, the interval since vaccination was between 1 and 25 days. There were five post-marketing reports of encephalopathy, with the time to onset of symptoms since the last dose of Pentacel reported as 1, 5, 7, 10, and 24 days, respectively. Most cases of encephalopathy had an identified plausible cause other than vaccination. In two cases, influenza A virus was isolated from nasopharyngeal secretions. One case each was associated with bloody diarrhea, atypical Kawasaki syndrome, and complex symptoms 24 days post-vaccination. In interpreting these data, the characteristics of passive surveillance systems should be considered. For example, passive surveillance for adverse events is subject to underreporting; serious, life-threatening events and fatal cases are more likely to be reported than minor events; and events with a shorter onset time after vaccination are more likely to be reported than those with a longer interval since vaccination.

The BLA also included publications from a hospital-based Canadian program of active surveillance for post-vaccination adverse events. Participating hospitals, of which there are currently 12, encompass approximately 90% of Canada's tertiary care pediatric beds and serve an immediate population base of 3 million children (approximately half of Canada's population under 15 years of age). Based on vaccine distribution data, vaccine coverage rates, and hospitalizations for encephalopathy and encephalitis at participating sites during the period 1993-2002, the risk, if any, of developing encephalopathy or encephalitis as a result of vaccination was estimated as <1 per 3 million doses of whole-cell pertussis

vaccine and <1 per 3.5 million doses of acellular pertussis vaccine (Pentacel for Doses 1-4 and Sanofi Pasteur's DTaP-IPV for Dose 5). In addition, data from this active surveillance system suggested a decreased risk of febrile seizures and HHEs with the introduction of Pentacel in Canada in place of whole-cell DTP vaccines.

Within the constraints of the sample sizes of the pivotal safety studies, the available data did not raise any particular concerns with regard to the occurrence of adverse events following Pentacel relative to separately administered Control vaccines and no concerning safety signals were identified. However, given the number of subjects evaluated, the ability of the pivotal studies safety database to evaluate rare adverse events is limited. While the limitations of passive surveillance systems, particularly underreporting, are well recognized, the available data on spontaneous post-marketing reports of adverse events following Pentacel provide some assurance of the overall safety of Pentacel in the general population. Data from the Canadian hospital-based program of active surveillance for certain targeted vaccine adverse events also provide some assurance of the safety of Pentacel with regard to febrile seizures, HHEs and encephalopathy.

In conclusion, the available safety data from the pivotal clinical studies and the supportive safety data from historical studies and from post-marketing use of Pentacel, primarily in Canada , support the safety of Pentacel in children 6 weeks to 4 years of age. The safety data in the BLA support use of Pentacel as a four dose series, with a single dose intramuscularly administered at 2, 4, 6 and 15-18 months of age. Use of Pentacel in children 19 months through 4 years of age is intended for catch-up immunization for unvaccinated children and children whose vaccinations have been delayed. Safety of Pentacel in children 19 months through 4 years of age is supported by clinical evidence of the safety of Pentacel in children 6 weeks to 18 months of age. Based on the justification provided in Section 8.3 of CBER's Clinical Safety Review of Pentacel, waiver of the requirement, under the Pediatric Research Equity Act, to conduct studies of Pentacel in infants 0 to 5 weeks of age and children 5 to 16 years of age is recommended. FDA's Pediatric Review Committee concurred with this recommendation.

Based on current recommendations for DTaP vaccination, children who receive a four dose series with Pentacel will need a fifth dose of DTaP vaccine at age 4 to 6 years. Since some State immunization requirements for school entry specify receipt of the last dose of IPV after the fourth birthday, some children who receive the recommended four dose IPV series with Pentacel may be required to receive an extra dose of IPV.

The applicant has proposed to conduct a descriptive post-licensure passive surveillance study designed to detect serious adverse events and specified, medically-attended neurological conditions, hypersensitivity reactions, and new-onset autoimmune disease following Pentacel. The proposed study will accrue at least 10,000 children who receive Pentacel and an unspecified number of children who receive other DTaP vaccines. For each subject, passive surveillance for specified adverse events through 6 months following the fourth dose of Pentacel or other DTaP vaccine will be conducted by review of computerized medical records and state mortality tapes. This study will also provide safety data on concomitant use of Rotavirus vaccine and Pentacel. In view of the available pre-licensure clinical data on Pentacel and the post-marketing data on use of Pentacel outside the U.S., the proposed study, combined with routine pharmacovigilance activities, is considered sufficient for the post-marketing safety evaluation of Pentacel.

The applicant has committed to submit safety data to support the use of DAPTACEL in children 4-6 years of age following four previous doses of Pentacel.

Bio Research Monitoring Review
Four bioresearch monitoring inspections were conducted. The results of these inspections noted protocol

deviations and missing data (see July 21, 2006 summary by J. White). Data discrepancies are noted in the clinical and immunogenicity reviews.

Advisory Committee Meeting

Pentacel was discussed during the Vaccines and Related Biological Products Advisory Committee Meeting on January 25, 2007. The committee voted that the safety data were adequate to support the safety of a four dose series of Pentacel administered to infants and children. The committee voted that the immunogenicity data were adequate to support the effectiveness of Pentacel although several members expressed concern regarding effectiveness of the Hib and pertussis components and advocated post-licensure surveillance for invasive Hib disease and pertussis.

Pediatrics

Pentacel was discussed during the PeRC meeting on May 14, 2008. The committee concurred with OVRR's recommendation that use of Pentacel in children 19 months through 4 years of age was supported by clinical evidence of safety and effectiveness (immunogenicity) in children 6 weeks to 18 months of age. The committee concurred with OVRR's recommendation to waive pediatric study requirements for birth to 5 weeks (before age 6 weeks) and 5-16 years (5 years to prior to 17 th birthday).
(see April 25, 2008 memo to PeRC)

Labeling

There were no special labeling issues. Labeling was jointly agreed upon with input from APLB (M. Gallagher) and others in OVRR.

Post-marketing Activities

Sanofi pasteur have committed to provide:

1. Clinical data to support use of DAPTACEL® to complete the DTaP series following four previous doses of Pentacel®.
2. ----------
3. ----------
4. A final report for Study M5A10
5. A final report for Study M5A07
6. ----------

Sanofi pasteur will perform the following activities:

1. In coordination with the Centers for Disease Control and Prevention (CDC) sanofi pasteur will report CDC surveillance data on cases of invasive *Haemophilus influenzae* type b (Hib) disease among children 0-4 years of age identified by the Active Bacterial Core Surveillance program for at least 6 years. In conjunction with this surveillance program, sanofi pasteur will conduct sample surveys to provide brand-specific vaccine exposure data and calculate product-specific rates of

invasive Hib disease within the monitored population.

2. In coordination with the ---------- and the Wisconsin Department of Health and Family Services sanofi pasteur will report surveillance data on cases of pertussis among children less than 5 years of age in the State of Wisconsin, over at least 5 years. In conjunction with this surveillance program, using data from the Wisconsin vaccine registry, sanofi pasteur will provide brand-specific vaccine exposure data and calculate product-specific rates of pertussis within the monitored population.
3. A descriptive study of the safety of Pentacel® with regard to selected medically attended events in at least 10,000 infants who will be followed from the first dose of Pentacel through approximately 6 months after the fourth dose.

Recommendation:

Approval.

Footnotes

1 Robbins JB, Parke JC, Schneerson R. Quantitative measurement of "natural" and immunization-induced *Haemophilus influenzae* type b capsular polysaccharide antibodies. Pediatr Res 1973;7:103

2 Kayhty H, et al. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. J Infect Dis 1983;147:1100

3 Anderson P. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. J Infect Dis 1984;149:1034

* Among the 5,980 subjects who received at least one dose of Pentacel in the pivotal studies, one subject randomized to receive Control vaccines received Pentacel for the first dose and Control vaccines for Doses 2-4. In calculating rates of events across doses and across studies, this subject was included in the randomized Control group. Thus, for such analyses, 5,979 subjects are included in the Pentacel group.

Updated: July 10, 2008

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE COMMISSIONER OF PATENTS AND TRADEMARKS

In re Astra Lakemedel Aktiebolag	:	REQUEST FOR PATENT
U.S. Patent No. 4,529,601	:	TERM EXTENSION
	:	
_____	:	FINAL DECISION

An application for extension of the term of U.S. Patent No. 4,529,601 has been filed under 35 USC § 156. The application raises a question of eligibility for patent term extension of a patent claiming two active ingredients in a drug product (EMLA Cream) that was approved for commercial marketing and use by the Food and Drug Administration (FDA), where each of the active ingredients had been approved separately for commercial marketing and use in previous regulatory reviews by the FDA. For the reasons set forth below, the application is denied.

Facts

The application for extension of the term of U.S. Patent No. 4,529,601 granted July 16, 1985, which claims a human drug product containing a specific mixture (by weight) of lidocaine and prilocaine, was filed in the Patent and Trademark Office (PTO) on February 26, 1993. The application was filed by the patent owner Astra Lakemedel Aktiebolag (Astra).

EMLA Cream is a drug product that was approved for commercial marketing and use by the FDA on December 12, 1992, pursuant to § 505 of the Federal Food, Drug and Cosmetic Act. The approved product, a homogeneous cream which contains a mixture of lidocaine and prilocaine in specified weight proportions, was approved as a topical anesthetic for local anesthesia. Lidocaine and prilocaine are well known anesthetics, each of which had previously been independently approved as a topical anesthetic for local anesthesia.

The '601 patent claims prilocaine in admixture with lidocaine in a specified weight ratio. Astra admits (Appl., p. 2) that lidocaine and prilocaine have previously been approved by the FDA as separate compounds, but submits that the claimed product sets forth a distinct and novel active ingredient. Astra argues the active ingredient in EMLA Cream is "the eutectic mixture that results from combining lidocaine and prilocaine in the specified weight proportions." Astra asserts:

> The novelty of this active ingredient is demonstrated by the synergistic effect of the resulting eutectic mixture in the form of an oil which gives EMLA Cream improved deep penetrating effects and improved anesthesia which surpasses the topical anesthetic effect of either lidocaine or prilocaine alone when each is administered as a separate compound [or] when administered together in two different formulations (Appl., p. 2).

On August 31, 1993, Astra submitted a letter (with Attachments A-C and Exhibits A1-A6) in support of the application for extension. In the letter Astra repeats its contention that EMLA Cream contains a new distinct and novel active ingredient. Astra states that both lidocaine base and prilocaine base exist in crystalline form at room temperature, but when the crystalline bases of lidocaine and prilocaine are mixed with each other a physio-chemical change takes place and a eutectic mixture results in the form of an oil that has a melting point below room temperature, and therefore, both lidocaine and prilocaine exist as a liquid oil rather than as crystals . Astra asserts that this oil constitutes the new distinct and novel active ingredient. Astra states that this is because once the oil is formed, the individual ingredients, lidocaine and prilocaine, are no longer physically distinguishable, and that individually, lidocaine and prilocaine do not penetrate the intact skin to produce anesthesia but EMLA Cream readily penetrates the intact skin to produce anesthesia.

Astra further argues that the FDA recognized the single active ingredient character of EMLA Cream because it waived its fixed combination prescription drug policy as defined in 21 CFR § 300.50 on the ground that the mixture is sufficiently unique that an exception to satisfy the combination drug policy seems warranted. Astra states on page 6 of the letter:

> By waiving the applicability of the fixed combination drug policy the FDA acknowledged that EMLA Cream does not have two active ingredients. Rather, EMLA Cream has a new distinct and novel active ingredient, a eutectic mixture in the form of an oil which is created when a physico-chemical change takes place upon mixing the crystalline forms of lidocaine base with prilocaine base. Thus, EMLA Cream meets the requirements of Section 156.

Discussion of Eligibility Criteria For Patent Term Extension

The starting point for statutory interpretation is the plain language of the statute. Unless it is ambiguous, the language Congress chose is conclusive of its meaning absent a clearly stated contrary intention. Burlington Northern R.R. v. Oklahoma Tax Comm'n, 481 U.S. 454, 461 (1987). See also Glaxo Operations UK Ltd. v. Quigg, 894 F2d 392, 395, 13 USPQ2d 1628, 1630 (Fed. Cir. 1990) (absent a "clearly expressed legislative intention to the contrary," a statute's plain meaning "must ordinarily be regarded as conclusive"). Statutory words are normally presumed, unless the contrary appears, to be used in their ordinary and usual sense, and with the meaning commonly attributed to them. Calminetti v. United States, 242 U.S. 470, 485 (1917) (the meaning of a statute must, in the first instance, be sought in the language in which the act is framed and, if that is plain, the sole function of the court is to enforce it according to its terms).

Under 35 USC § 156(a) a term of a patent which claims a product shall be extended if, inter alia, the product has been subject to a regulatory review period before its commercial marketing or use. In addition, under § 156(a)(5)(A):

> ... the permission for the commercial marketing or use of the product ... is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred; (Emphasis added.)

Thus, the determination of eligibility of U.S. Patent No. 4,529,601 turns on the provisions in § 156(a)(5)(A) that the permission for the commercial marketing or use is the first permitted commercial marketing or use of the product. The term "product" is defined in 35 USC § 156(f) as follows:

> (f) For purposes of this section:
>
> (1) The term "product" means:
>
> (A) A drug product. ...
>
> (2) The term "drug product" means the active ingredient of -
>
> (A) a new drug ... (as those terms are used in the Federal Food, Drug and Cosmetic Act ...
>
> including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient. (Emphasis added.)

Where, as in the present case, no salts or esters of the active ingredients are involved, the definition of "product" set forth in § 156(f) (substituted within brackets for "product et seq." in § 156(a) and for "product" in § 156(a)(5)(A)) applies to the patent term extension requirements of §§ 156(a) and 156(a)(5)(A) as follows:

> § 156(a) The term of a patent which claims [the active ingredient ..., as a single entity or in combination with another active ingredient] ... shall be extended ... if -
>
> (5)(A) ... the permission for the commercial marketing or use of [the active ingredient ..., as a single entity or in combination with another active ingredient] after such regulatory review period is the first permitted commercial marketing or use of [the active ingredient ..., as a single entity or in combination with another active ingredient] under the provision of law under which such regulatory review period occurred;

The statute says active ingredient, not active ingredients. Thus, eligibility for patent term extension under § 156(a) requires that the patent claims the active ingredient of a new drug, as a single entity or in combination with another active ingredient. Section 156(a)(5)(A) permits patent term extension based on FDA approval of the active ingredient as a single entity or in combination with another active ingredient, provided it is the first FDA approval of the active ingredient, as a single entity or in combination with another active ingredient.

For a product which contains a plurality of active ingredients, as here, the statute must be analyzed with respect to each active ingredient. Active ingredient, as defined in § 156(f), is singular and the definition of "human drug product" explicitly recognizes that the "active ingredient" may be used "in combination with another active ingredient" to embrace a human drug product with a combination of active ingredients. If the term "active ingredient" was interpreted to include a plurality of active ingredients, the phrase "including any salt or ester of the active ingredient" would not make any sense because there is no such thing as a salt or ester of two ingredients. A statute should be construed, if possible, to avoid absurd results. United States v. Turkette, 452 U.S. 576 (1981).

Application of Eligibility Criteria to '601 Patent and EMLA Cream

The following facts are either admitted by Astra or supported by the record: (1) the active ingredient lidocaine was previously approved under § 505 for obtaining local anesthesia; (2) the

active ingredient prilocaine was previously approved under § 505 for obtaining local anesthesia; and, (3) EMLA Cream is the first product that contains both the active ingredients lidocaine and prilocaine to be approved under § 505 for obtaining local anesthesia.

The determination of eligibility of the '601 patent for patent term extension turns on the provisions of § 156(a)(5)(A). Astra argues the combination of lidocaine and prilocaine in the specified weight proportions is a new "active ingredient" which was approved for the first time. The FDA advises the PTO that EMLA Cream was approved through a regulatory review period as a product containing the two previously approved "active ingredients" lidocaine and prilocaine rather than as a new chemical entity resulting from the combination of these active ingredients. In a letter dated August 4, 1993, the FDA states:

> The active ingredients in EMLA Cream, lidocaine and prilocaine, have both been previously approved and EMLA Cream contains no new chemical entity. In fact, EMLA Cream was approved through a regulatory review period, as defined under 35 U.S.C. § 156(a)(4), based on the fact that EMLA Cream is a product containing the two previously-approved drugs of lidocaine and prilocaine rather than as a new chemical entity resulting from these active ingredients. Therefore, the applicant's claim that EMLA Cream presents a "distinct and novel active ingredient" does not appear to be supported by FDA's records. [Emphasis added.]

The record does not support Astra's claim that a new active ingredient is present. Astra's assertion on page 2 of the application that the eutectic mixture of lidocaine and prilocaine in the form of an oil has a synergistic effect resulting in improved anesthesia surpassing the anesthesia effect of lidocaine and prilocaine alone or together in different formulations is contradicted by the reports and background materials contained in the record. In its telefax transmission to the FDA on August 23, 1989, describing the analgesic effectiveness of EMLA Cream (Exh. A-4, ¶ 4), Astra states:

> It is known ... that both drug substances [lidocaine and prilocaine] penetrate the epidermis and enter the dermis of the skin where ... pain receptor nerve endings ... are located. No claim is made for any synergistic action or for any other pharmacological interaction between the two active local anesthetics. The only implied claim is that both agents contribute in some degree to the block of neuronal structures in the skin .... [Emphasis added.]

Astra's claim that a new active ingredient is present in EMLA Cream is further diluted in its letter of November 1, 1989, to the FDA (Exh. A-5, p. 2):

> It may be useful to keep in mind that EMLA is a formulation of two thoroughly studied and widely used local anesthetics. ... EMLA is able to act effectively at considerably reduced doses of lidocaine and prilocaine simply because its eutectic nature makes for a more efficient percutaneous migration of these substances. The lidocaine and prilocaine remain the same (as in other formulations) in every chemical particular; and the amounts of these substances available systemically from recommended doses of EMLA 5% Cream are similar to those systemically available from doses of these substances approved for relatively simple and routine dentistry. [Emphasis added.]

Astra further argues that the fact that the FDA decided to waive its fixed combination drug policy (21 CFR § 300.50) shows that the FDA acknowledged that EMLA Cream does not have two active ingredients. The Combination Drug Policy of § 300.50 is used in determining the type of evidence required for approval of fixed combination drugs. A decision to waive the requirements of § 300.50 is not tantamount to a holding that no combination of drugs is present. If no combination were present, § 300.50 would not be applicable and there would be no reason to waive the rule. The record (Exh. A-4, ¶¶ 8-16) clearly shows that Astra, in response to the FDA's request for a comparison study of EMLA Cream, a lidocaine cream and a prilocaine cream, argued that such comparative testing would not be valid comparison because of the compositions of the respective creams. Astra points out that EMLA Cream contains no solvent oil which is present in both lidocaine and prilocaine creams, which oil plays a role in the release rate of the anesthetic. In response to Astra's arguments, the FDA (Attachment C) decided that because, inter alia, of the apparent difficulty in obtaining an appropriate single ingredient control preparation (Attachment C, ¶ E), the mixture is sufficiently unique and an exception to satisfying the Combination Drug Policy seemed warranted. The FDA's subsequent decision not to require the proposed comparative study did not constitute a decision that a new active ingredient was present in EMLA Cream and no combination was present. On the contrary, because the FDA saw a need to apply (and, in the present case, waive) § 300.50, shows the FDA considered EMLA Cream to be a combination with lidocaine and prilocaine both present, but that the unique nature of the combination warranted a waiver of § 300.50.

The '601 patent claims the combination of active ingredients lidocaine and prilocaine contained in EMLA Cream. Under § 156(a)(5)(A), as it pertains to the active ingredients claimed in the patent (lidocaine and prilocaine), the patent would be eligible for patent term extension if:

> ... the permission for the commercial marketing or use of [the active ingredient ... , as a single entity (either lidocaine or prilocaine) or in combination with another active ingredient (either lidocaine or prilocaine in combination with another active ingredient)] after such regulatory review period is the first permitted commercial marketing or use of [the active ingredient ... , as a single entity (either lidocaine or prilocaine) or in combination with another active ingredient (either lidocaine or prilocaine in combination with another active ingredient)] under the provision of law [§ 505 of the Act] under which such regulatory review period occurred;

Here, the patent is not eligible because each of the active ingredients claimed in the patent and present in the approved product (lidocaine and prilocaine) previously were permitted to be commercially marketed and used under the same provision of law [§ 505 of the Act] under which such regulatory review period for EMLA Cream occurred. The approval of EMLA Cream did not represent the first permitted commercial marketing or use of either of the active ingredients in EMLA Cream under § 505 of the Act.

The fact that the approval of EMLA Cream represents the first time that the combination of lidocaine and prilocaine was permitted to be commercially marketed or used by the FDA does not give rise to eligibility for patent term extension. The statute is clear that patent term extension is permitted under § 156(a)(5)(A) only if the approval of the active ingredient is the first approval of the active ingredient - i.e., no previous approvals of the active ingredient have occurred as a single entity or in combination with another active ingredient. As noted above, both lidocaine and prilocaine have been approved by the FDA as single entities prior to the approval of EMLA Cream. Clearly, the approval of EMLA Cream does not represent the first approval of either lidocaine or prilocaine.

Legislative History Supports the PTO Position

The '601 patent is not eligible for patent term extension because the permission for commercial marketing or use of EMLA Cream was not the first permitted commercial marketing or use of the active ingredients claimed in the patent within the meaning of §156(a)(5)(A). This position is consistent with the statute, including the statutory definition of the term "product" in § 156(f), and the legislative history of the statute.

From the beginning of the congressional debate that led to enactment of § 156, attention focused on the decline of effective patent life for new chemical entity (NCE) drugs. In re Alcon Laboratories Inc., 13 USPQ2d 1115, 1119 (Comm'r Pats 1989). Congress adopted the focus on NCE's when it proscribed patent term extension [§ 156(a)(5)(A)] if the active ingredients had received permission for commercial marketing or use in regulatory review periods that were concluded prior to a subsequent regulatory review period upon which the application for patent term extension is based. If the active ingredients had already received permission for commercial marketing from the FDA under the same provision of law, they would not be considered to be an NCE in a subsequent regulatory review period whether the active ingredients are used alone or in combination with other active ingredients. According to a report by the House Committee on Energy and Commerce accompanying H.R. 3605, 98th Cong., 2d Sess. (1983):

> Paragraphs [(a)(4)] and [(a)(5)] describe two conditions which must be met by the product which is claimed in the product patent to be extended .... First, the product must have been subjected to a regulatory review period under an applicable federal law, and approved, before the product was allowed to be commercially marketed. ... Second, ... the approved product must have been approved for commercial marketing for the first time. The Committee's bill requires extensions to be based on the first approval of a product because the only evidence available to Congress showing that patent time has been lost is data on so-called class I, new chemical entity drugs. These drugs had been approved by the Food and Drug Administration (FDA) for the first time. (Emphasis added.)

H.R. Rep. No. 98-857, Part I, 98th Cong., 2d Sess. 37-38 (1984), reprinted in 1984 U.S. Code Cong. & Admin. News 2671.

The legislative history shows that Congress intended that the condition expressed in § 156(a)(5)(A) should apply to the product [active ingredients] claimed in the patent [§ 156(a)], and that patent term extension should be available only to active ingredients that are NCE's which have been approved by the FDA for the first time. The only evidence showing that patent time had been lost in the regulatory review process before the FDA related to NCE drugs.

Thus, the legislative history of § 156 shows that Congress intended to grant patent term extension only to those products [active ingredients] classified by the FDA as class I new chemical entities under FDA's long-standing drug classification system. [A copy of the FDA

Staff Manual Guide No. CDER 4820.3, dated January 22, 1992, describing the IND/NDA Classification System is attached to this decision.] According to this classification system, Type I drugs are new molecular entities - i.e., the active moiety (that part of the chemical compound that is responsible for the drug's therapeutic effect) is not yet marketed either as a single entity or as part of a combination product. Type 1 drugs are contrasted to other types which are directed to new salts, esters or derivatives of active moieties (Type 2), new formulations (Type 3), new combinations of drugs not previously marketed together (Type 4), already marketed drug products (Types 5 and 6) and drugs already marketed but without an approved NDA (Type 7). These Types are not mutually exclusive, but where the drug product falls into more than one category, all appropriate categories are reflected in the overall classification for the drug.

Congress found no evidence relating to new combinations of old active ingredients, old active ingredients administered in a new dosage form and no evidence relating to an old active ingredient approved for a new indication (use) that would justify patent term extension based on products of these types. As noted in Fisons plc v. Quigg, 876 F.2d 99, 10 USPQ2d 1869 (Fed. Cir. 1989), there is strong support in the legislative history of § 156 for the interpretation of § 156(a)(5)(A) adopted by the PTO that patent term extension is available only to drug products that are NCEs - i.e., active ingredients that have been approved for the first time by the FDA.

Each of the active ingredients lidocaine and prilocaine contained in the approved product EMLA Cream was a well known local anesthetic that had been independently approved for commercial marketing and use prior to FDA approval of EMLA Cream for use as a local anesthetic. Since both active ingredients had been previously approved, neither lidocaine, prilocaine, nor their combination was a new chemical/molecular entity at the time of FDA approval of EMLA Cream.

Accordingly, it is consistent with the legislative history of § 156 that a patent claiming a combination of two active ingredients, both of which were previously approved as local anesthetics, be denied patent term extension based on a later approval of a drug product containing the combination for use as a local anesthetic, notwithstanding any enhanced effect of the combination.

Decision

The PTO concludes that U.S. Patent No. 4,529,601, which claims a combination of the active ingredients lidocaine and prilocaine in the approved product EMLA Cream, is not eligible for patent term extension under § 156. Accordingly, the application for extension is denied because the permission for commercial marketing or use of lidocaine and prilocaine in EMLA Cream was not the first permitted commercial marketing or use of lidocaine or prilocaine under the provision of law [§ 505 of the Federal Food, Drug and Cosmetic Act] under which regulatory review of EMLA Cream occurred. 35 USC § 156(a)(5)(A).

Date: 03 March 1994

C. E. Van Horn

Charles E. Van Horn
Patent Policy & Projects Administrator
Office of the Assistant Commissioner for Patents

Edward V. Filardi
White & Case
1155 Avenue of the Americas
New York, NY 10036-2787

(For Astra)

cc: Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 11-44
Rockville, MD 20857

Re: EMLA Cream

FDA Docket No. 93E - 0130